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APPLICATION NUMBER: ***60/544,944***
FILING DATE: ***February 14, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/04630***

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
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15992 U.S. PTO
021404

PTO/SB/16 (08-03)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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15535 U.S. PTO
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021404

INVENTOR(S)

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☒ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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City		State		ZIP	
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ENCLOSED APPLICATION PARTS ***(check all that apply)***

☒ Specification *Number of Pages* 54

☐ CD(s), Number ____

☐ Drawing(s) *Number of Sheets* ____

☒ Other (specify) Fee Transmittal (1 page); Return Postcard

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

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☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): 160

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ____.

Respectfully submitted,
SIGNATURE Scott W Reid

Date 2/14/2004

TYPED or PRINTED NAME Scott W. Reid

REGISTRATION NO. (*if appropriate*) 48,097

Docket Number: P1126US00

TELEPHONE 858-812-1796

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION COVER SHEET
Additional Page

PTO/SB/16 (08-03)
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Docket Number P1126US00

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Number 1 of 1

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 160

Complete if Known	
Application Number	
Filing Date	14 February 2004
First Named Inventor	Ha-Soon CHOI
Examiner Name	
Art Unit	
Attorney Docket No.	P1126US00

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 50-1885

Deposit Account Name: THE GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	160
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filling fee	

SUBTOTAL (1) ($) 160

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20 ** =	0	X		=	0
Independent Claims		-3 ** =	0	X		=	0
Multiple Dependent				X		=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 0

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Scott W. Reid	*Registration No. (Attorney/Agent)*	48,097	*Telephone*	858-812-1796
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Express Mail Label No.: EV 417300518 US
Date of Deposit: 14 February 2004
I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to: Mail Stop Provisional Patent Application, Commissioner for Patents PO Box 1450, Alexandria, VA 22313-1450

By: Scott W. Reid
Scott W. Reid

Docket No: P1126US00

United States Provisional Patent Application

COMPOUNDS AND COMPOSITIONS AS PROTEIN KINASE INHIBITORS

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AS FILED IN USPTO ON 14 FEBRUARY 2004

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COMPOUNDS AND COMPOSITIONS AS PROTEIN KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly diseases or disorders that involve abnormal activation of the FAK, Abl, BCR-Abl, PDGF-R, c-Kit, Flt-3 and c-Met kinases.

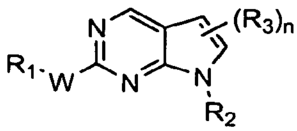
Background

The protein kinases represent a large family of proteins, which play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. A partial, non-limiting, list of these kinases include: receptor tyrosine kinases such as platelet-derived growth factor receptor kinase (PDGF-R), the receptor kinase for stem cell factor, c-kit, the nerve growth factor receptor, trkB, c-Met, and the fibroblast growth factor receptor, FGFR3; non-receptor tyrosine kinases such Abl and the fusion kinase BCR-Abl, focal adhesion kinase (FAK), Fes, Lck and Syk; and serine/threonine kinases such as b-RAF, MAP kinases (e.g., MKK6) and SAPK2β. Aberrant kinase activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune and nervous systems.

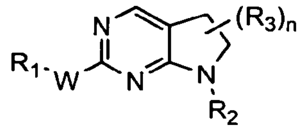
The novel compounds of this invention inhibit the activity of one or more protein kinases and are, therefore, expected to be useful in the treatment of kinase-associated diseases.

SUMMARY OF THE INVENTION

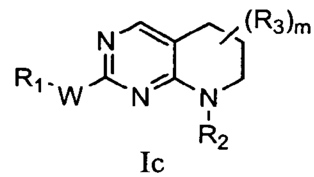
In one aspect, the present invention provides compounds chosen from Formulae Ia, Ib, Ic, Id and Ie:



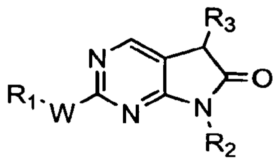
Ia



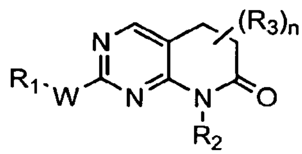
Ib



Ic



Id



Ie

in which:

n is chosen from 0, 1 and 2; m is chosen from 0, 1, 2 and 3;

W is chosen from $-NR_4-$, $-S-$, $-O-$, $-S(O)-$ and $-S(O)_2-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl;

R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XNR_5R_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent of R_1 is further optionally substituted by 1 to 5 radicals independently chosen from C_{1-6}alkyl and C_{1-6}alkoxy;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XSNR_5R_5$, $-XS(O)NR_5R_5$, $-XS(O)_2NR_5R_5$, $-XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5R_5$, $-$

$XC(O)NR_5XC(O)OR_5$, $-XC(O)NR_5XNR_5C(O)R_5$, $-XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; and R_7 is cyano;

R_3 is chosen from halo, hydroxy, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)R_5$ and $-XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

In a third aspect, the present invention provides a method of treating a disease in an animal in which inhibition of kinase activity, particularly FAK, Abl, BCR-Abl, PDGF-R, c-Kit, c-Met, trkB, FGFR3, Fes, Lck, Syk, b-RAF, MKK6 and/or SAPK2β activity, can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which kinase activity, particularly FAK, c-Met, Abl, BCR-Abl, PDGF-R, c-Kit, trkB, FGFR3, Fes, Lck, Syk, b-RAF, MKK6 and/or SAPK2β activity, contributes to the pathology and/or symptomology of the disease.

In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-4}-alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

"Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl may be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or $-S(O)_2-$, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 1,1-dioxo-116-thiomorpholin-4-yl, etc.

"Halogen" (or halo) preferably represents chloro or fluoro, but may also be bromo or iodo.

"Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I as detailed in the Summary of the Invention. In one

embodiment, with reference to compounds of Formula Ia, Ib, Ic, Id and Ie, W is chosen from –NR_4– and –O–; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl.

In a further embodiment, R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, C_{5-10}heteroaryl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, –XNR_5R_5, –XOR_5, –XSR_5, –$XNR_5XNR_5R_5$, –XNR_5XOR_5, –$XC(O)NR_5R_5$, –$XOXR_6$ and –$XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and –C(O)OH; wherein any heteroaryl substituent of R_1 is further optionally substituted by 1 to 5 C_{1-6}alkyl radicals.

In a further embodiment, R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, C_{3-8}heteroarylC_{0-4}alkyl, –XNR_5R_5, –XOR_5, –XSR_5, –$XS(O)_2NR_5R_5$, –$XC(O)OR_5$, –$XOC(O)R_5$, –$XC(O)NR_5XNR_5R_5$, –$XC(O)NR_5XC(O)OR_5$, –$XC(O)NR_5XNR_5C(O)R_5$, –$XC(O)NR_5XNR_5C(O)OR_5$, –$XC(O)NR_5XOR_5$, –$XC(O)N(XOR_5)_2$, –$XNR_5C(O)R_5$, –$XC(O)NR_5R_6$, –$XC(O)R_6$, –XR_7, –XR_6 and –$XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and –C(O)OH; and R_7 is cyano.

In a further embodiment, R_3 is chosen from halo, hydroxy, –$XC(O)R_5$ and –$XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl.

In a further embodiment, W is chosen from –NH– and –O–; and R_1 is chosen from phenyl, benzyl, 5,6,7,8-tetrahydro-naphthalenyl, benzo[1,3]dioxolyl, 1H-indazol-7-yl, indan-4-yl and 1H-indolyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from methoxy, methyl, amino, halo, hydroxymethyl, hydroxy, quinoxalinyl, ethyl, pyridinyl, methoxy-phenyl, piperazinyl-carbonyl, ethyl-(2-hydroxy-ethyl)-amino 2-(4-methyl-piperazin-1-yl)-ethoxy, formamyl, isopropyl, methyl-sulfanyl, tri-fluoro-methyl, ethoxy, 3-isopropylamino-propylamino, dimethyl-amino, morpholino, cyclopropyl-methoxy, butoxy, cycloheptyl-oxy and 1,4,5,7-tetramethyl-pyrrolo[3,4-d]pyridazinyl.

In a further embodiment, R_2 is chosen from pyridinyl, phenyl, thiazolyl, pyridinyl-methyl, pyridinyl-ethyl, thiophenyl, benzyl, quinolinyl, 7-oxo-5,6,7,8-tetrahydro-naphthalenyl, naphthyl and pyrimidinyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, methyl, propyl-sulfamoyl, methyl-sulfamoyl, methoxy, methyl-carboxy, 2-dimethylamino-ethyl-formamyl, carboxy, amino, cyano-ethyl, cyano-methyl, ethenyl, tri-fluoro-methyl, hydroxy-methyl, ethyl, methyl-sulfanyl, butyl, isobutyl, carboxy-methyl-formamidyl, 1-carboxy-ethyl-formamidyl, carboxy-ethyl, amino-ethyl-formamidyl, amino-propyl-formamidyl, dimethyl-amino-ethyl-formamidyl, dimethyl-amino-propyl-formamidyl, dimethyl-amino-butyl-formamidyl, methyl-formamidyl, ethyl-formamidyl, ethyl-formamidyl-methyl, 2-(2-dimethylamino-ethylcarbamoyl)-ethyl, 2-(2-dimethylamino-formamidyl)-ethyl, 2-(amino-ethyl-formamidyl)-ethyl, 2-(amino-propyl-formamidyl)-ethyl, 2-(propyl-formamidyl)-ethyl, amino-propyl-formamidyl-methyl, 2-(methyl-amino-carbamoyl)-ethyl, 2-(ethyl-amino-carbamoyl)-ethyl, morpholino-ethyl-formamidyl, morpholino-carbonyl-methyl, amino-ethyl-formamidyl-methyl, cyclobutyl-formamidyl, methyl-formamidyl-methyl, dimethyl-formamidyl-methyl, hydroxy-ethyl-formamidyl-methyl, hydroxy-propyl-formamidyl-methyl, N,N-bis-(3-hydroxy-propyl)-formamidyl, cyclopentyl-formamidyl, isobutyl-formamidyl, isobutyl-formamidyl-methyl, cyclopentyl-formamidyl-methyl, cyano-ethyl-formamidyl, cyano-methyl-formamidyl, pyrrolidinyl-ethyl-formamidyl, 2-(isobutyl-formamidyl)-ethyl, 1H-tetrazolyl, 2-(1H-tetrazol-5-yl)-ethyl, 2-(1H-tetrazol-5-yl)-methyl, 2-(1-methyl-1H-tetrazol-5-yl)-methyl, acetyl-amino, cyclopropyl-formamidyl-methyl, hydroxy-ethyl-formamidyl, hydroxy-propyl-formamidyl, propyl-formamidyl-methyl, ethoxy-propyl-formamidyl, acetyl-amino-ethyl-formamidyl, 1-methyl-piperidin-4-yl-formamidyl, morpholino-carbonyl-ethyl, methoxy-carbonyl-methyl, methoxy-carbonyl-ethyl-formamidyl, methoxy-carbonyl-ethyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl, 4-amino-cyclohexyl-formamidyl, 4-amino-cyclohexyl-formamidyl-methyl, acetyl-amino-ethyl-formamidyl-methyl, ethoxy-propyl-formamidyl-methyl, methoxy-carbonyl-ethyl, 1-formyl-pyrrolidin-2-yl-carboxylic acid, (1-carboxy-3-methyl-butyl)-formamidyl, 2-(methoxy-carbonyl-methyl-formamidyl)-ethyl, 1-carboxy-(2,2-dimethyl-propyl)-formamidyl, 3-tert-butoxycarbonyl-amino-propyl-formamidyl, acetoxy-methyl and 1-carboxy-ethyl-formamidyl.

In a further embodiment, n is 0 or 1; m is 0 or 1; and R_3 is chosen from halo, hydroxy, –C(O)OH and –C(O)OCH_3.

Preferred compounds of Formula I are detailed in the Examples and Table I, *infra*.

Pharmacology and Utility

Compounds of the invention modulate the activity of protein tyrosine kinases and, as such, are useful for treating diseases or disorders in which protein tyrosine kinases, particularly FAK, c-Met, Abl, BCR-Abl, PDGF-R, c-Kit, trkB, FGFR3, Fes, Lck, Syk, b-RAF, MKK6 and SAPK2β kinases, contribute to the pathology and/or symptomology of the disease.

Focal adhesion kinase (FAK), a non-receptor protein-tyrosine kinase, is localized to cell substratum-extracellular matrix (ECM) contact sites that function as part of a cytoskeletal-associated network of signaling proteins (Schlaepfer, et al., Prog. Diophys., Mol., 1999, 71, 435-478. In adherent cells, FAK is often associated with integrins at focal adhesions (Schlaepfer, et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 5192- 5196). Phosphorylation of FAK results in activation of the mitogen-activated protein kinase pathway. Overexpression of FAK is involved in cancer progression. High levels of FAK correlate with invasiveness and metastatic potential in colon tumors (Weiner, T.M., et al., Lancet, 1993, 342, 1024-1025), breast tumors (Owens, L.V., et al., Cancer Res., 1995, 55, 2752-2755) and oral cancers (Kornberg, L. J., Head Neck, 1998, 20, 634-639). The role of FAK in cell migration has led to the speculation that it may be relevant in other diseases such as embryonic development dysfunctions and angiogenic disorders (Kornberg, L. J., Head Neck, 1998,20,634-639).

Abelson tyrosine kinase (i.e. Abl, c-Abl) is involved in the regulation of the cell cycle, in the cellular response to genotoxic stress, and in the transmission of information about the cellular environment through integrin signaling. Overall, it appears that the Abl protein serves a complex role as a cellular module that integrates signals from various extracellular and intracellular sources and that influences decisions in regard to cell cycle and apoptosis. Abelson tyrosine kinase includes sub-types derivatives such as the chimeric fusion (oncoprotein) BCR-Abl with deregulated tyrosine kinase activity or the v-Abl. BCR-Abl is critical in the pathogenesis of 95% of chronic myelogenous leukemia (CML) and 10% of acute lymphocytic leukemia. STI-571 (Gleevec) is an inhibitor of the oncogenic BCR-Abl tyrosine kinase and is used for the treatment of chronic myeloid leukemia (CML). However, some patients in the blast

crisis stage of CML are resistant to STI-571 due to mutations in the BCR-Abl kinase. Over 22 mutations have been reported to date with the most common being G250E, E255V, T315I, F317L and M351T.

Compounds of the present invention inhibit abl kinase, especially v-abl kinase. The compounds of the present invention also inhibit wild-type BCR-Abl kinase and mutations of BCR-Abl kinase and are thus suitable for the treatment of Bcr-abl-positive cancer and tumor diseases, such as leukemias (especially chronic myeloid leukemia and acute lymphoblastic leukemia, where especially apoptotic mechanisms of action are found), and also shows effects on the subgroup of leukemic stem cells as well as potential for the purification of these cells *in vitro* after removal of said cells (for example, bone marrow removal) and reimplantation of the cells once they have been cleared of cancer cells (for example, reimplantation of purified bone marrow cells).

PDGF (Platelet-derived Growth Factor) is a very commonly occurring growth factor, which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. Compounds of the invention can inhibit PDGF receptor (PDGFR) activity and are, therefore, suitable for the treatment of tumor diseases, such as gliomas, sarcomas, prostate tumors, and tumors of the colon, breast, and ovary.

Compounds of the present invention, can be used not only as a tumor-inhibiting substance, for example in small cell lung cancer, but also as an agent to treat non-malignant proliferative disorders, such as atherosclerosis, thrombosis, psoriasis, scleroderma and fibrosis, as well as for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluoruracil, and in asthma. Compounds of the invention can especially be used for the treatment of diseases, which respond to an inhibition of the PDGF receptor kinase.

Compounds of the present invention show useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as especially obliterative bronchiolitis (OB), i.e. a chronic rejection of allogenic lung transplants. In contrast to patients without OB, those with OB often show an elevated PDGF concentration in bronchoalveolar lavage fluids.

Compounds of the present invention are also effective in diseases associated with vascular smooth-muscle cell migration and proliferation (where PDGF and PDGF-R often also play a role), such as restenosis and atherosclerosis. These effects and the consequences thereof for the proliferation or migration of vascular smooth-muscle cells *in vitro* and *in vivo* can be demonstrated by administration of the compounds of the present invention, and also by investigating its effect on the thickening of the vascular intima following mechanical injury *in vivo*.

The compounds of the present invention also inhibit cellular processes involving stem-cell factor (SCF, also known as the c-kit ligand or steel factor), such as inhibiting SCF receptor (kit) autophosphorylation and SCF-stimulated activation of MAPK kinase (mitogen-activated protein kinase). MO7e cells are a human promegakaryocytic leukemia cell line, which depends on SCF for proliferation. Compounds of the invention can inhibit the autophosphorylation of SCF receptors.

The Ras-Raf-MEK-ERK signaling pathway mediates cellular response to growth signals. Ras is mutated to an oncogenic form in ~15% of human cancer. The Raf family belongs to the serine/threonine protein kinase and it includes three members, A-Raf, B-Raf and c-Raf (or Raf-1). The focus on Raf being a drug target has centered on the relationship of Raf as a downstream effector of Ras. However, recent data suggests that B-Raf may have a prominent role in the formation of certain tumors with no requirement for an activated Ras allele (Nature 417, 949 - 954 (01 Jul 2002). In particular, B-Raf mutations have been detected in a large percentage of malignant melanomas.

Existing medical treatments for melanoma are limited in their effectiveness, especially for late stage melanomas. The compounds of the present invention also inhibit cellular processes involving b-Raf kinase, providing a new therapeutic opportunity for treatment of human cancers, especially for melanoma.

In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required

dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting

or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations may also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations). For example, synergistic effects can occur with other immunomodulatory, anti-inflammatory or any substances used in the treatment of the diseases mentioned above, for example when used in combination with cyclosporin, rapamycin, or ascomycin, or immunosuppressant analogues thereof, for example cyclosporin A (CsA), cyclosporin G, FK-506, rapamycin, or comparable compounds, corticosteroids, cyclophosphamide, azathioprine, methotrexate, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate mofetil, 15-deoxyspergualin, immunosuppressant antibodies, especially monoclonal antibodies for leukocyte receptors, for example MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands, or other immunomodulatory compounds, such as CTLA41g. Where the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

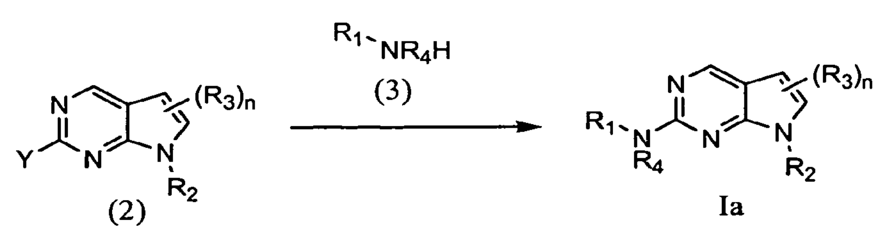
The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Compounds of Formula I, in which W is $-NR_4-$, can be prepared by proceeding as in the following Reaction Scheme I:

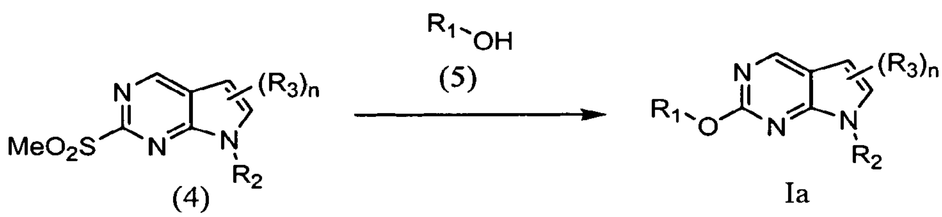
Reaction Scheme I



in which R_1, R_2, R_3, R_4 and n are as defined for Formula I in the Summary of the Invention and Y is a leaving group such as halogen (e.g. chloro, and the like). A compound of Formula Ia can be prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable base (e.g., potassium tertiary butoxide and diisopropylethyl amine, and the like), a suitable solvent (e.g., 1,4-dioxane and butanol, and the like). The reaction is carried out at 50 to 130°C and can take up to 4 hours to complete. Similarly, using appropriate starting materials, reaction with a compound of formula 3 results in compounds of Formula Ib, Ic, Id and Ie.

Compounds of Formula I, in which W is –O–, can be prepared by proceeding as in the following Reaction Scheme II:

Reaction Scheme II



in which R_1, R_2, R_3, R_4 and n are as defined for Formula I in the Summary of the Invention. A compound of Formula Ia can be prepared by reacting a compound of formula 4 with a compound of formula 5 in the presence of a suitable solvent (e.g., DMSO, and the like) and a suitable base (e.g., potassium tertiary butoxide, and the like). The reaction is carried out at 50 to 130 °C and can take up to 4 hours to complete.

Detailed descriptions of the synthesis of a compound of Formula I can be found in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with

a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.)

Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically

pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of reaction schemes I or II; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

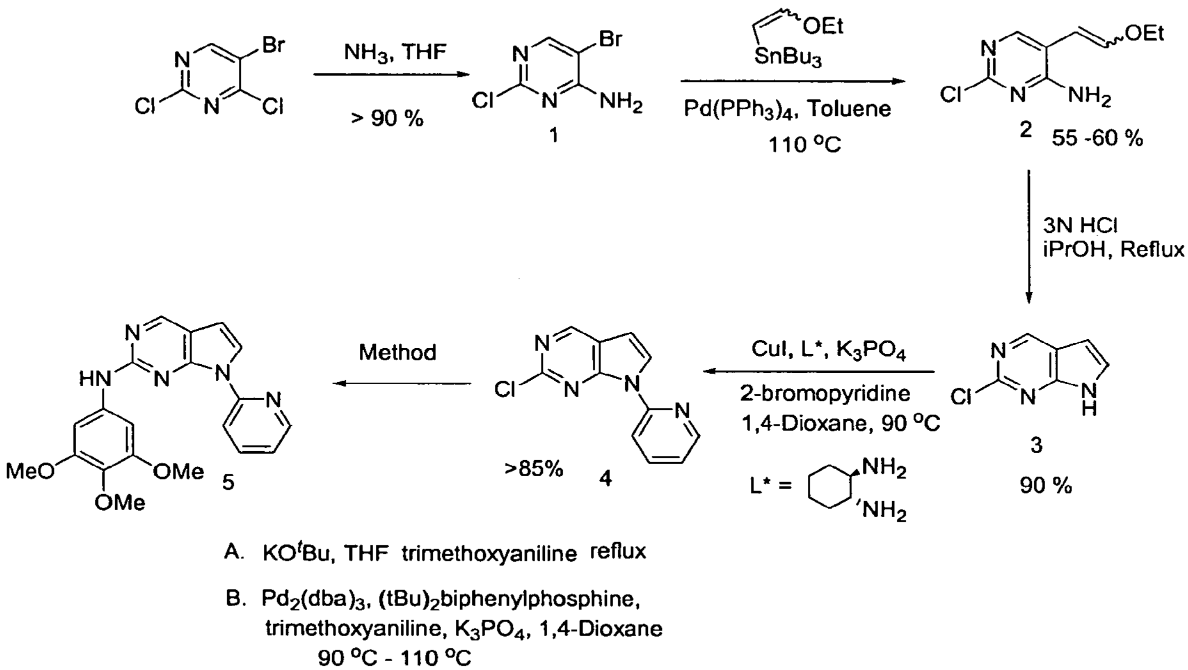
Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I (Examples) and intermediates (References) according to the invention.

Example 1



Synthesis of 5-Bromo-2-chloropyrimidin-4-ylamine (1): A solution of 5-bromo-2,4-dichloropyrimidine (25g, 110 mmol) in 200 mL THF is treated with 47 mL of ammonia (330 mmol, 7.0M solution in methanol). After stirring for 15 hours the solution is concentrated under reduced pressure and purified by short-filtration (SiO_2, Hexanes : Ethyl acetate / 1:1) to yield 21g (92 %) of **1** as a white solid.

Synthesis of 2-Chloro-5-(2-ethoxyvinyl)-pyrimidin-4-ylamine (2): A 500 mL round bottomed flask is charged with 5-bromo-2-chloropyrimidin-4-ylamine (1) (10g, 48 mmol), tetrakis(triphenylphosphine)palladium(0) (2.8g, 2.5 mmol), and toluene (200 mL). Tributyl-(2-ethoxyvinyl)-stannane (22g, 60 mmol) is added and the reaction heated to 110^{0}C with stirring for approximately 15 hours. After cooling to room temperature, the solution is diluted with 100 mL ethyl acetate and washed with water and brine. The organic extract is dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, Hexane : Ethyl acetate / 5 :1) provides **2** (4.4 g, 46%) as a yellow solid.

Synthesis of 2-Chloro-*7H*-pyrrolo-[2,3-*d*]pyrimidine 3: A 500 mL round bottomed flask was charged with 2-Chloro-5-(2-ethoxyvinyl)-pyrimidin-4-ylamine **2** (4.4g, 20 mmol). Isopropanol (200 mL) is added followed by 25 mL of concentrated hydrochloric acid. The solution is heated to 90^{0}C and stirred for two hours. After cooling to room temperature, the solution is concentrated under reduced pressure then basified to pH 9 with saturated aqueous $NaHCO_3$. The aqueous layer is extracted with ethyl acetate, and the organic extracts are combined and washed with saturated aqueous $NaHCO_3$ and brine. The organic extracts are dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by short-filtration (SiO_2, Hexanes : Ethyl acetate / 1 : 1) gives **3** (3.1g, 92%) as a white solid.

Synthesis of 2-Chloro-7-pyridin-2-yl-*7H*-pyrrolo-[2,3-*d*]pyrimidine 4: A suspension of 2-chloro-*7H*-pyrrolo-[2,3-*d*]pyrimidine **3** (0.53g, 3.5 mmol), 2-bromopyridine (0.66 mL, 1.1g, 6.9 mmol), copper(I) iodide (0.20g, 1.0 mmol), *trans*-1,2-diaminocyclohexane (0.12 mL, 0.11g, 1.0 mmol), and potassium phosphate (2.2 g, 10 mmol) in 10 mL 1,4-dioxane is heated to 100^{0}C and stirred for four hours. The reaction mixture is cooled to room temperature, diluted with ethyl acetate, and washed with water and brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, Hexane : Ethyl acetate / 5:1) provided **4** (0.69g, 87%) as a white solid.

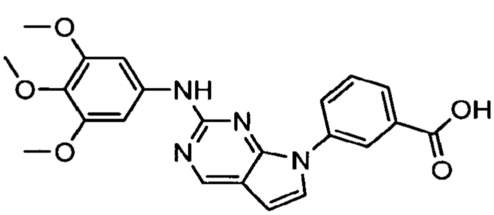
Synthesis of (7-Pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine (5):

Method 1. To a solution of 2-chloro-7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidine in 1,4-dioxane is added 3,4,5-trimethoxy aniline (3 equivalents) followed by adding potassium *tert*-butoxide solution (1.0 M in tetrahydrofuran, 3 equivalents) dropwise. After addition, the reaction mixture is heated at 80°C for 2 hours. The solvent is removed after cooling to room temperature. Purification by reverse phase HPLC gives (7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine as a white solid.

Method 2. A round bottle flask charged with 2-chloro-7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidine, 0.1 equivalents of tri(dibenzylideneacetone)dipalladium(0), 0.2 equivalents of biphenyl-2-yl-di-tert-butyl-phosphane, 3 equivalents of potassium phosphate and 1.5 equivalents of 3,4,5-trimethoxy aniline is flashed with nitrogen followed by the addition of 1,4-dioxane. The suspension is heated at 110°C for 18 hours. Filtration through a pad of Celite removed the solid. The filtrate is diluted with ethyl acetate, and washed with water and brine. After drying over magnesium sulfate, the product is concentrated and purified by chromatography (ethyl acetate: hexanes 1:1) to give 7-pyridin-2-yl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-(3,4,5-trimethoxy-phenyl)-amine as a white solid.

Example 2

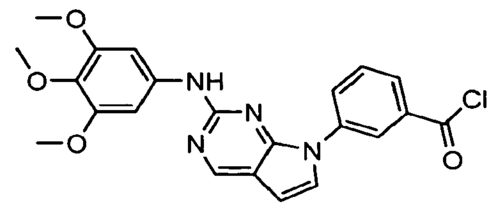
3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid



A solution of 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid methyl ester in 1N sodium hydroxide (methanol: water 1:1) is stirred at room temperature for 15 hours. Acidification with 1N hydrochloric acid to pH 6 gives a precipitate. Filtration and washing with water gives 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid as a white solid.

Example 3

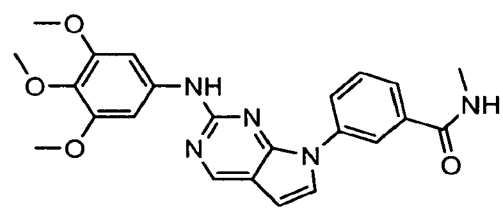
3-[2-(3,4,5-Trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoyl chloride



A dry round bottle flask charged with 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoic acid is flushed with nitrogen, dichloromethane and a few drops of *N,N'*-dimethylformamide are added. Oxalyl chloride solution (2.0 M in dichloromethane) is added dropwise. The reaction mixture is stirred at room temperature for 30 minutes, resulting in a solution of 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoyl chloride.

Example 4

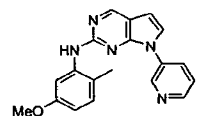
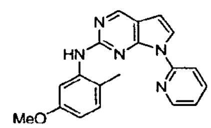
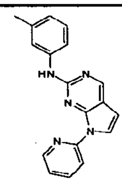
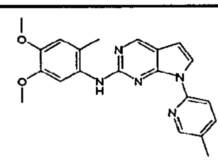
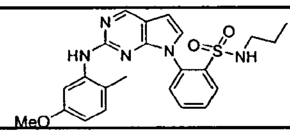
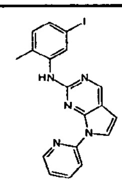
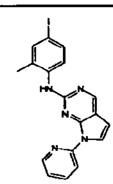
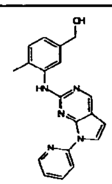
N-Methyl-3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide

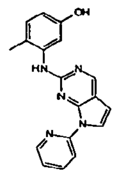
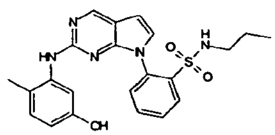
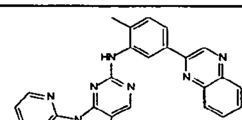
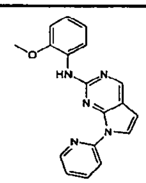
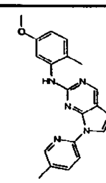
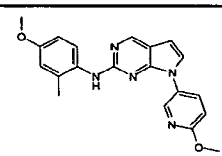
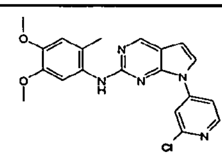
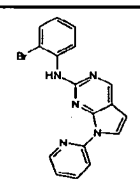
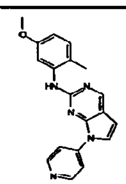


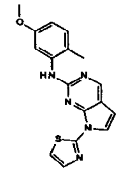
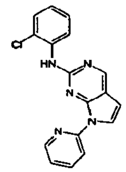
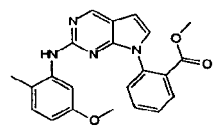
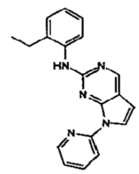
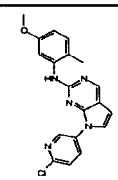
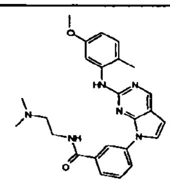
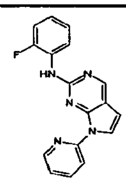
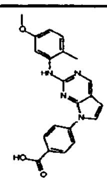
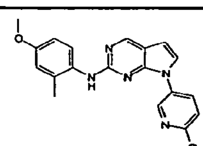
To a solution of 3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzoyl chloride in dichloromethane is added 5 equivalents of methylamine solution (2.0 M in tetrahydrofuran). After stirring at room temperature for 1 hour, the reaction is quenched with water. Removal of the solvent followed by purification with reverse phase HPLC gives *N*-methyl-3-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide as a white solid.

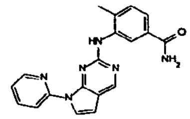
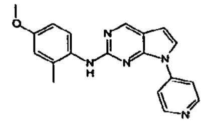
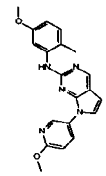
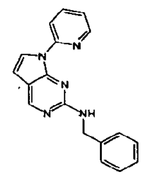
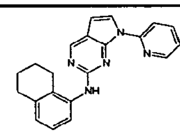
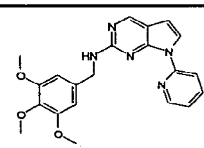
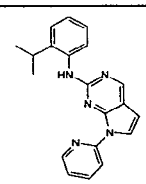
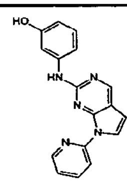
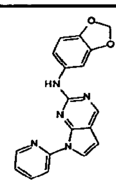
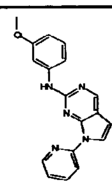
By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

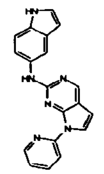
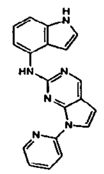
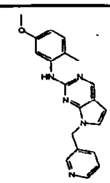
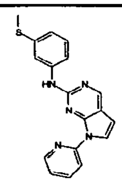
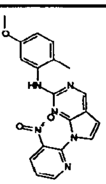
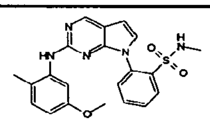
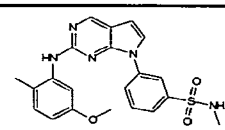
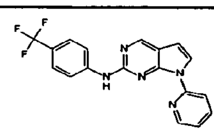
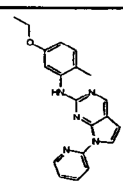
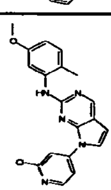
Table 1

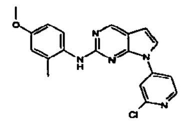
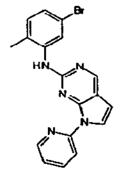
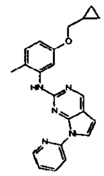
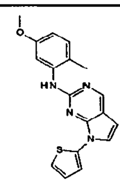
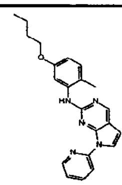
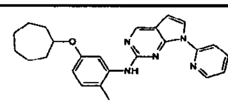
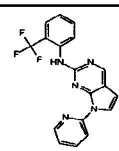
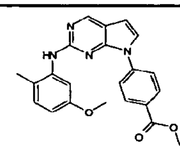
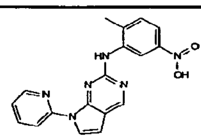
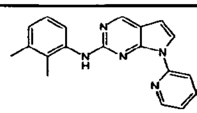
Compound Number	Structure	Physical Data ^{1}H NMR and MS (m/z)
1		MS *(m/z)* 332.3 (M+1)
2		MS *(m/z)* 332.2 (M+1)
3		MS (*m/z*) 302.2 (M+1)
4		MS (*m/z*) 376.3 (M+1)
5		MS (*m/z*) 452.2 (M+1)
6		MS (*m/z*) 428.1 (M+1)
7		MS (*m/z*) 428.1 (M+1)
8		MS (*m/z*) 332.2 (M+1)

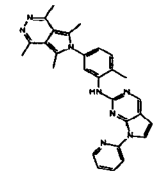
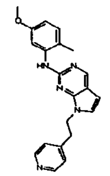
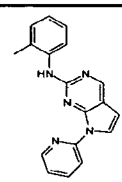
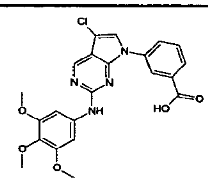
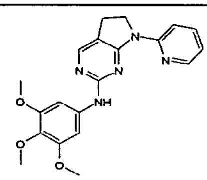
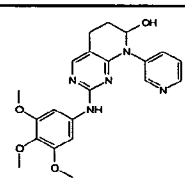
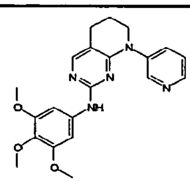
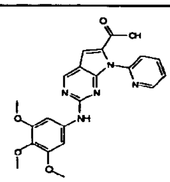
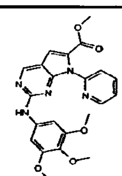
9		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.68 (s, 1H), 8.32 (m, 2H), 8.05 (d, 1H), 7.73 (m, 1H), 7.14 (m, 1H), 6.80 (d, 1H), 6.62 (d, 1H), 6.36 (d, 1H), 6.23 (m, 1H); MS (*m/z*) 318.2 (M+1).
10		^{1}H NMR 400 MHz ($CDCl_3$) δ 10.35 (s, 1H), 8.52 (s, 1H), 8.07 (dd, 1H), 7.70 (m, 2H), 7.37 (dd, 1H), 7.24 (d, 1H), 7.10 (d, 1H), 6.94 (d, 1H), 6.68 (d, 1H), 6.52 (dd, 1H), 5.28 (b, 1H), 3.02 (m, 2H), 2.16 (s, 3H), 1.27 (m, 2H), 0.76 (t, 3H); MS (*m/z*) 438.2 (M+1).
11		MS (*m/z*) 430.2 (M+1).
12		MS (*m/z*) 418.2 (M+1).
13		MS (*m/z*) 436.2 (M+1).
14		MS (*m/z*) 362.3 (M+1).
15		MS (*m/z*) 396.2 (M+1).
16		MS (*m/z*) 366.1 (M+1).
17		MS (*m/z*) 332.3 (M+1).

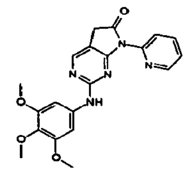
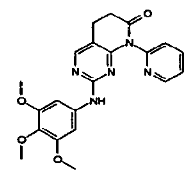
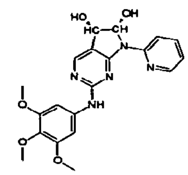
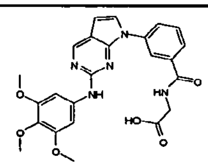
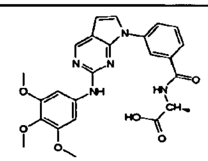
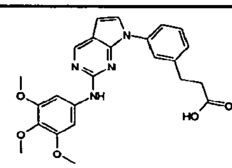
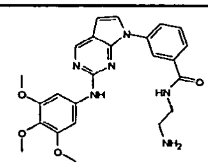
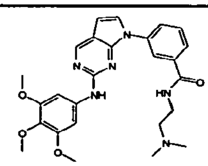
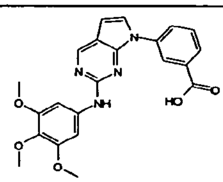
18		MS (*m/z*) 338.3 (M+1).
19		MS (*m/z*) 306.2 (M+1).
20		MS (*m/z*) 389.2 (M+1).
21		MS (*m/z*) 316.2 (M+1).
22		MS (*m/z*) 366.1 (M+1).
23		MS (*m/z*) 445.2 (M+1).
24		MS (*m/z*) 306.1 (M+1).
25		MS (*m/z*) 375.2 (M+1).
26		MS (*m/z*) 366.1 (M+1).

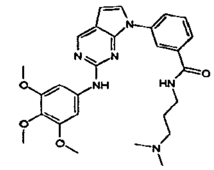
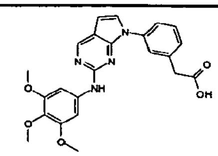
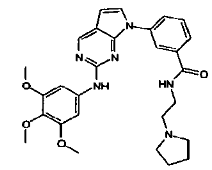
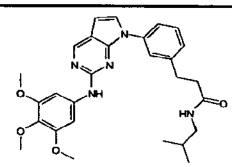
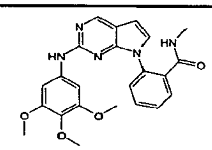
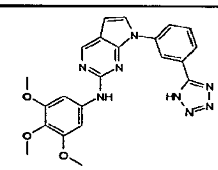
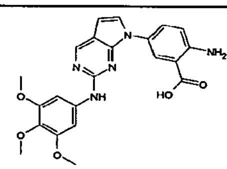
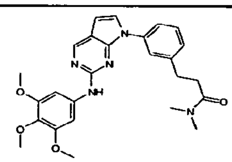
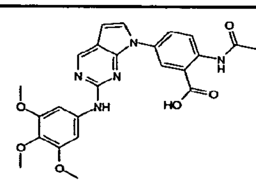
27		MS (m/z) 345.2 (M+1).
28		MS (m/z) 332.1 (M+1).
29		MS (m/z) 362.2 (M+1).
30		MS (m/z) 302.1 (M+1).
31		MS (m/z) 342.2 (M+1).
32		MS (m/z) 392.2 (M+1).
33		MS (m/z) 330.2 (M+1).
34		MS (m/z) 304.1 (M+1).
35		MS (m/z) 332.1 (M+1).
36		MS (m/z) 318.1 (M+1).

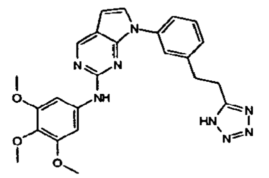
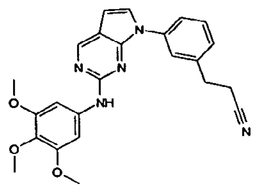
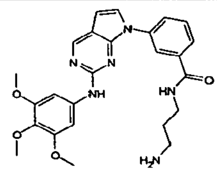
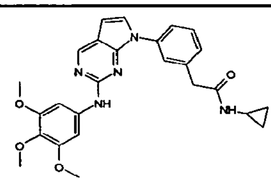
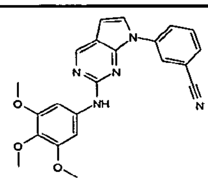
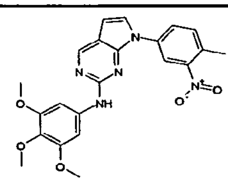
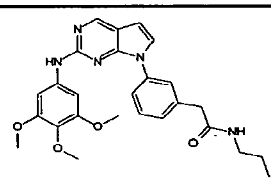
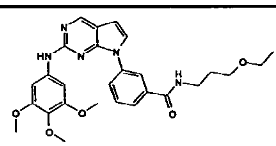
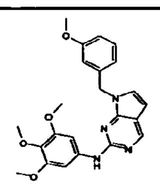
37		MS (*m/z*) 327.1 (M+1).
38		MS (*m/z*) 327.1 (M+1).
39		MS (*m/z*) 346.2 (M+1).
40		MS (*m/z*) 334.1 (M+1).
41		MS (*m/z*) 377.1 (M+1).
42		MS (*m/z*) 424.2 (M+1).
43		MS (*m/z*) 424.2 (M+1).
44		MS (*m/z*) 356.1 (M+1).
45		MS (*m/z*) 346.2 (M+1).
46		MS (*m/z*) 366.1 (M+1).

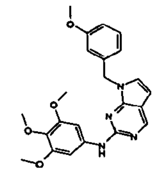
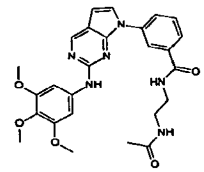
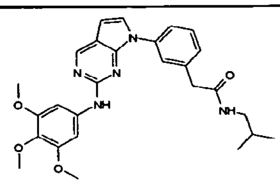
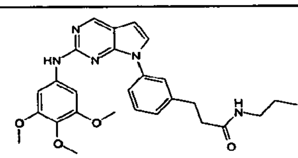
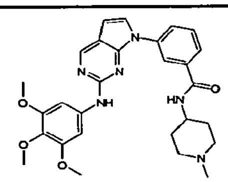
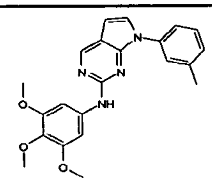
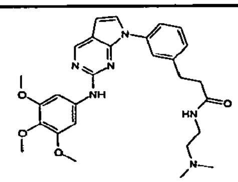
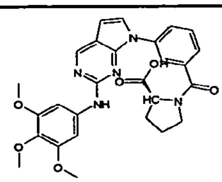
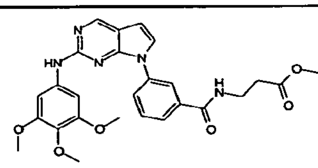
47		MS (*m/z*) 366.1 (M+1).
48		MS (*m/z*) 380.1 (M+1).
49		MS (*m/z*) 372.2 (M+1).
50		MS (*m/z*) 337.1 (M+1).
51		MS (*m/z*) 374.2 (M+1).
52		MS (*m/z*) 414.2 (M+1).
53		MS (*m/z*) 356.1 (M+1).
54		MS (*m/z*) 389.2 (M+1).
55		MS (*m/z*) 347.2 (M+1).
56		MS (*m/z*) 316.2 (M+1).

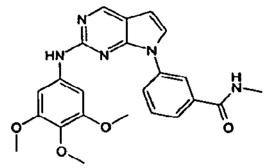
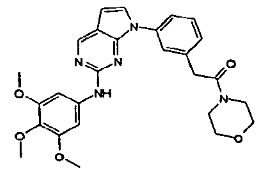
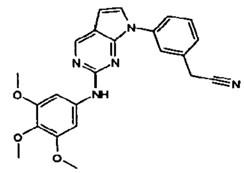
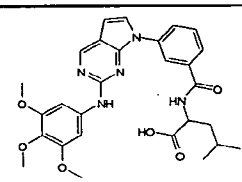
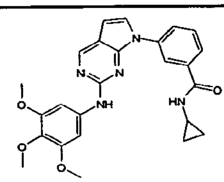
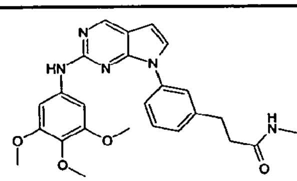
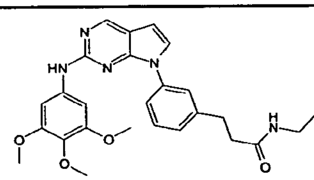
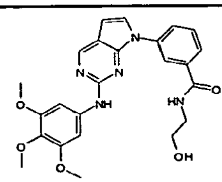
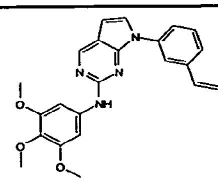
57		MS (*m/z*) 475.2 (M+1).
58		MS (*m/z*) 360.2 (M+1).
59		MS (*m/z*) 302.2 (M+1).
60		MS (*m/z*) 375.2 (M+1).
61		MS (*m/z*) 379.9 (M+1).
62		MS (*m/z*) 410.5 (M+1).
63		MS (*m/z*) 394.4 (M+1).
64		MS (*m/z*) 422.1 (M+1).
65		MS (*m/z*) 436.2 (M+1).

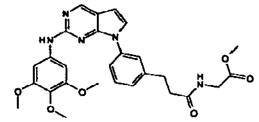
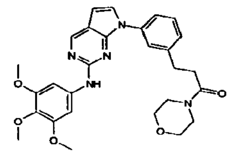
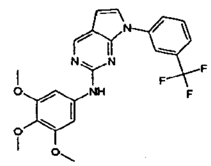
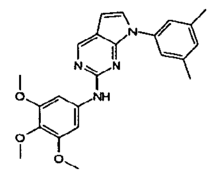
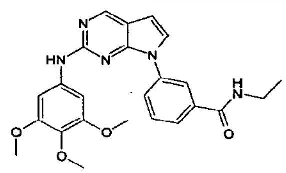
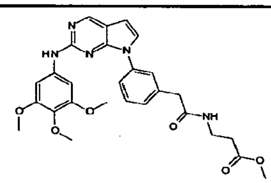
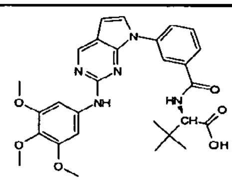
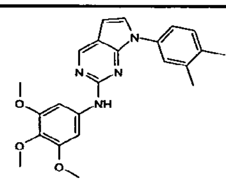
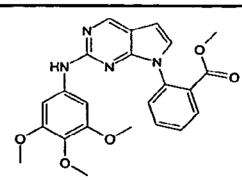
66		MS (*m/z*) 394.4 (M+1).
67		MS (*m/z*) 408.4 (M+1).
68		MS (*m/z*) 412.2 (M+1).
69		MS (*m/z*) 477.8 (M+1).
70		MS (*m/z*) 492.2 (M+1).
71		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.31 (s, 1H), 8.75 (s, 1H), 7.65 (m, 1H), 7.53 (s, 1H), 7.51 (d, 1H), 7.39 (t, 1H), 7.21 (m, 1H), 7.13 (s, 2H), 6.61 (d, 1H), 5.83 (s, 1H), 3.53 (d, 9H), 2.85 (m, 2H), 2.54 (m,2H); MS (*m/z*) 449.0 (M+1).
72		MS (*m/z*) 463.2 (M+1).
73		MS (*m/z*) 491.2 (M+1).
74		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.30 (s, 1H), 8.73 (s, 1H), 8.13 (m, 1H), 8.02 (m, 1H), 7.87 (m, 1H), 7.59 (t, 1H), 7.55 (d, 1H), 7.09 (s, 2H), 6.61 (d, 1H), 5.77 (s, 1H), 3.48 (d, 9H); MS (*m/z*) 421.1 (M+1).

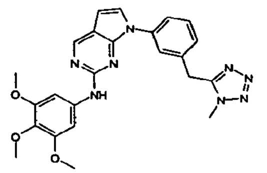
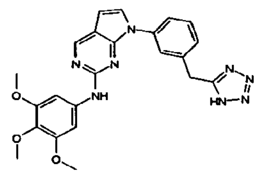
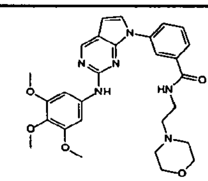
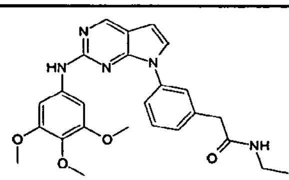
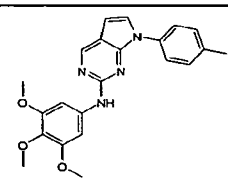
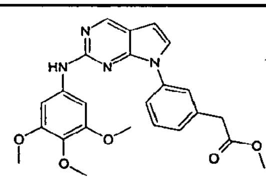
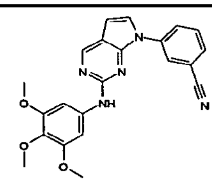
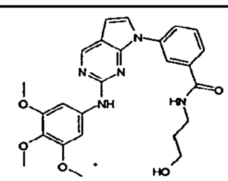
75		MS (m/z) 505.3 (M+1).
76		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.35 (s, 1H), 8.80 (s, 1H), 7.73 (d, 1H), 7.60 (s, 1H), 7.53 (d, 1H), 7.45 (t, 1H), 7.28 (d, 1H), 7.19 (s, 2H), 6.67 (d, 1H), 3.59 (m, 11H); MS (m/z) 435.2 (M+1).
77		MS (m/z) 516.3 (M+1).
78		MS (m/z) 504.3 (M+1).
79		MS (m/z) 434.2 (M+1).
80		^{1}H NMR 400 MHz (MeOH-d_4) δ 8.76 (s, 1H), 8.57 (t, 1H), 8.10 (m, 1H), 8.02 (m, 1H), 7.77 (m,2H), 6.97 (s, 2H), 6.86 (d, 1H), 3.69 (d, 9H); MS (m/z) 445.2 (M+1).
81		MS (m/z) 436.2 (M+1).
82		MS (m/z) 476.2 (M+1).
83		^{1}H NMR 400 MHz (DMSO-d_6) δ 11.17 (s, 1H), 9.53 (s, 1H), 8.94 (s, 1H), 8.72 (m, 1H), 8.33 (d, 1H), 8.17 (m, 1H), 7.71 (d, 1H), 7.32 (s, 2H), 6.81 (d, 1H), 3.72 (d, 9H), 2.33 (s, 3H); MS (m/z) 478.2 (M+1).

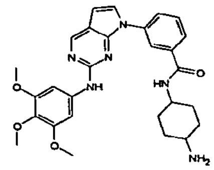
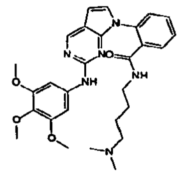
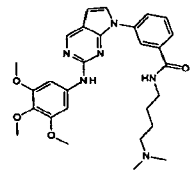
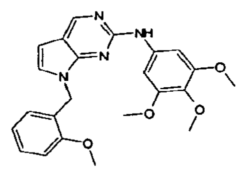
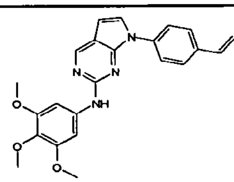
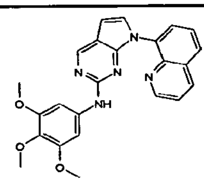
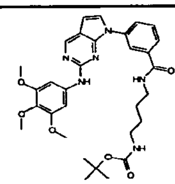
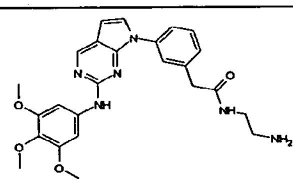
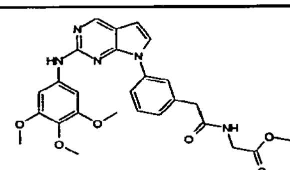
84		^{1}H NMR 400 MHz ($CDCl_3$) δ 11.6 (s, 1H), 8.48 (s, 1H), 7.69 (m, 1H), 7.46 (m, 2H), 7.33 (m, 1H), 7.25 (m, 1H), 6.73 (m, 3H), 3.98 (s, 3H), 3.66 (d, 6H), 3.09 (m, 2H), 2.92 (m, 2H); MS (*m/z*) 473.3 (M+1).
85		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.74 (s, 1H), 7.70 (m, 1H), 7.49 (t, 1H), 7.27 (d, 1H), 7.23 (m, 1H), 6.98 (d, 2H), 6.61 (d, 1H), 3.91 (s, 3H), 3.77 (s, 6H), 3.07 (m, 2H), 2.70 (m, 2H); MS (*m/z*) 430.2 (M+1).
86		MS (*m/z*) 477.2 (M+1).
87		MS (*m/z*) 474.2 (M+1).
88		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.67 (s, 1H), 8.02 (m, 2H), 7.55 (m, 2H), 7.16 (d. 1H), 6.86 (s, 2H), 6.56 (d, 1H), 3.85 (s, 3H), 3.72 (s, 6H); MS (*m/z*) 402.1 (M+1).
89		MS (*m/z*) 436.1 (M+1).
90		MS (*m/z*) 476.2 (M+1).
91		MS (*m/z*) 506.3 (M+1).
92		MS (*m/z*) 421.2 (M+1).

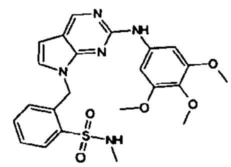
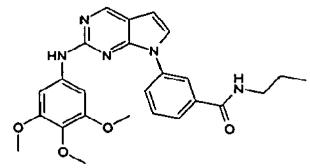
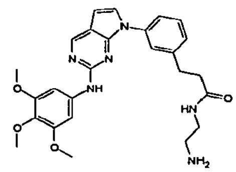
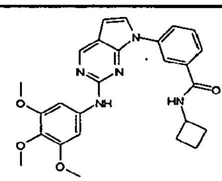
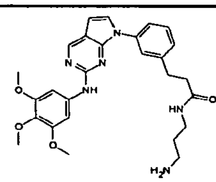
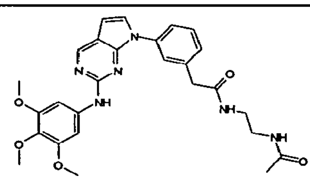
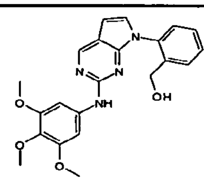
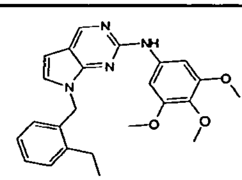
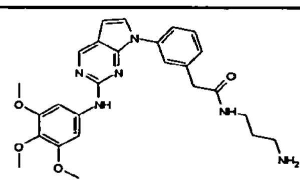
93		MS (*m/z*) 421.2 (M+1).
94		MS (*m/z*) 505.3 (M+1).
95		MS (*m/z*) 490.2 (M+1).
96		MS (*m/z*) 490.2 (M+1).
97		MS (*m/z*) 517.3 (M+1).
98		MS (*m/z*) 391.2 (M+1).
99		MS (*m/z*) 519.3 (M+1).
100		MS (*m/z*) 518.2 (M+1).
101		MS (*m/z*) 506.2 (M+1).

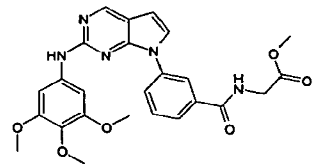
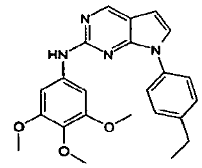
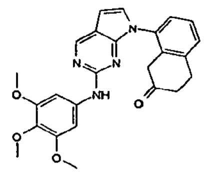
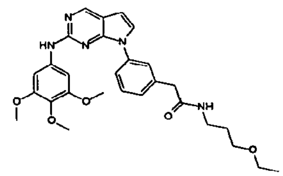
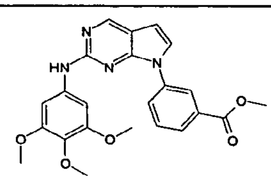
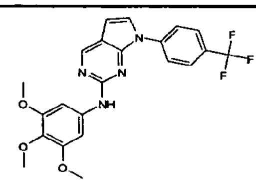
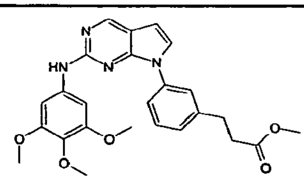
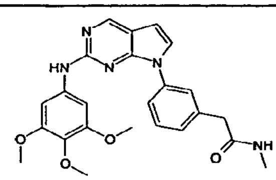
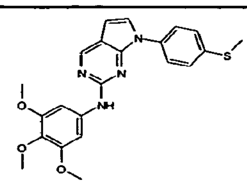
102		MS (*m/z*) 434.2 (M+1).
103		MS (*m/z*) 504.2 (M+1).
104		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.87 (s, 1H), 7.92 (m, 1H), 7.86 (m, 1H), 7.66 (t, 1H), 7.48 (m, 1H), 7.39 (d, 1H), 7.22 (s, 1H), 7.09 (s, 2H), 6.75 (d, 1H), 3.96 (s, 3H), 3.88 (s, 6H); MS (*m/z*) 415.9 (M+1).
105		MS (*m/z*) 534.2 (M+1).
106		MS (*m/z*) 460.2 (M+1).
107		MS (*m/z*) 462.2 (M+1).
108		MS (*m/z*) 476.2 (M+1).
109		MS (*m/z*) 464.2 (M+1).
110		MS (*m/z*) 445.1 (M+1).

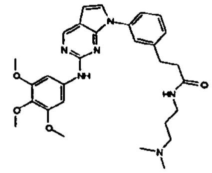
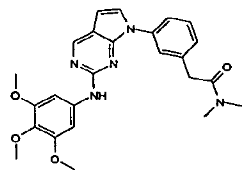
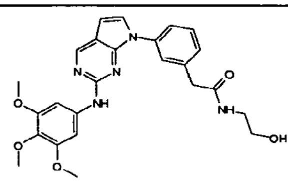
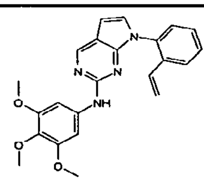
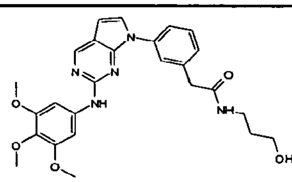
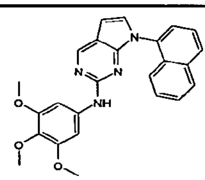
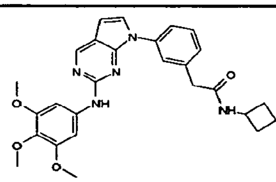
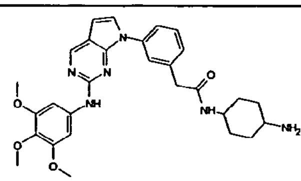
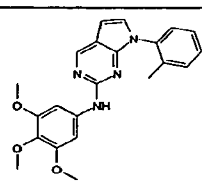
111		MS (*m/z*) 520.2 (M+1).
112		MS (*m/z*) 517.2 (M+1).
113		MS (*m/z*) 403.2 (M+1).
114		MS (*m/z*) 405.2 (M+1).
115		MS (*m/z*) 478.2 (M+1).
116		MS (*m/z*) 520.2 (M+1).
117		MS (*m/z*) 534.2 (M+1).
118		MS (*m/z*) 405.2 (M+1).
119		MS (*m/z*) 419.2 (M+1).

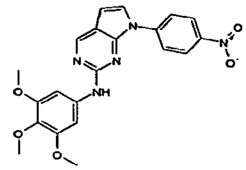
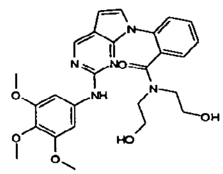
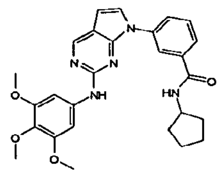
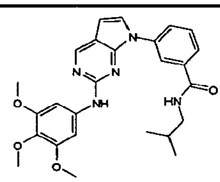
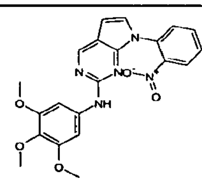
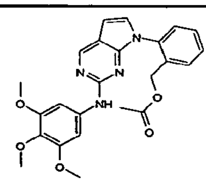
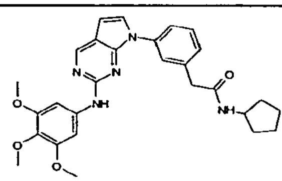
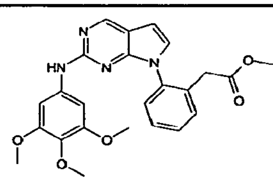
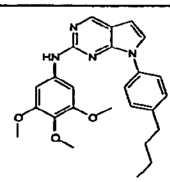
120		^{1}H NMR 400 MHz (MeOH-d_4) δ 8.61 (s, 1H), 7.64 (m, 2H), 7.49 (d, 1H), 7.43 (t, 1H), 7.22 (d, 1H), 6.90 (s, 2H), 6.63 (d, 1H), 4.31 (s, 2H), 3.90 (s, 3H), 3.62 (s, 3H), 3.56 (s, 6H); MS (*m/z*) 473.5 (M+1).
121		^{1}H NMR 400 MHz (MeOH-d_4) δ 8.62 (s, 1H), 7.65 (m, 1H), 7.63 (m, 1H), 7.54 (d, 1H), 7.43 (m, 1H), 7.26 (m, 1H), 6.86 (s, 2H), 6069 (d, 1H), 4.31 (s, 2H), 3.63 (s, 3H), 3.58 (s, 6H); MS (m/z) 415.9 (M+1). MS (*m/z*) 459.2 (M+1).
122		MS (*m/z*) 533.2 (M+1).
123		MS (*m/z*) 462.2 (M+1).
124		MS (*m/z*) 391.2 (M+1).
125		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.78 (s, 1H), 7.71 (m, 1H), 7.56 (m, 1H), 7.44 (t, 1H), 7.27 (m, 1H), 7.21 (d, 1H), 7.13 (b, 1H), 6.95 (s, 2H), 6.57 (d, 1H), 3.80 (s, 2H), 3.79 (s, 3H), 3.70 (m, 9H); MS (*m/z*) 449.3 (M+1).
126		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.67 (s, 1H), 8.04 (m, 1H), 8.01 (m, 1H), 7.55 (m, 2H), 7.16 (d, 1H), 7.07 (s, 1H), 6.87 (s, 2H), 6.57 (d, 1H), 3.76 (s, 3H), 3.71 (d, 6H); MS (*m/z*) 503.2 (M+1).
127		MS (*m/z*) 478.2 (M+1).

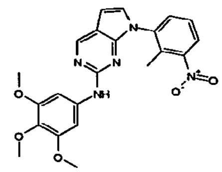
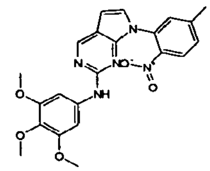
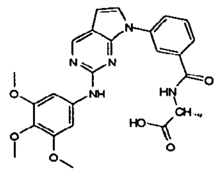
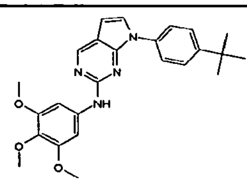
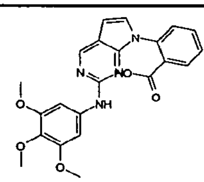
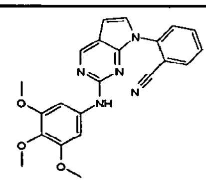
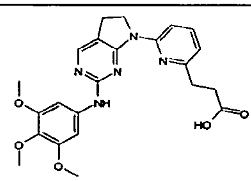
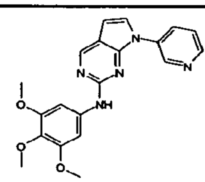
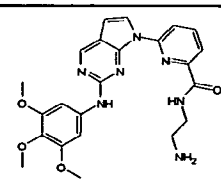
128		MS (*m/z*) 517.3 (M+1).
129		MS (*m/z*) 519.2 (M+1).
130		MS (*m/z*) 519.3 (M+1).
131		MS (*m/z*) 421.2 (M+1).
132		MS (*m/z*) 403.2 (M+1).
133		MS (*m/z*) 427.9 (M+1).
134		MS (*m/z*) 591.3 (M+1).
135		MS (*m/z*) 477.2 (M+1).
136		MS (*m/z*) 506.2 (M+1).

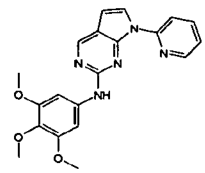
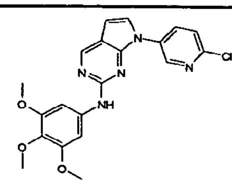
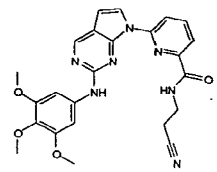
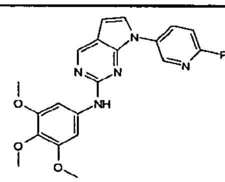
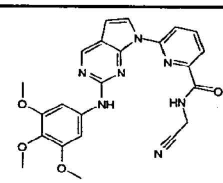
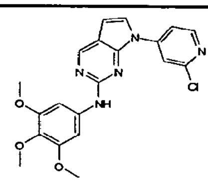
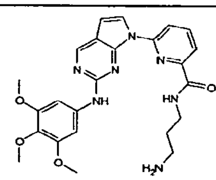
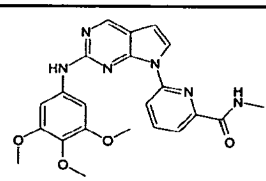
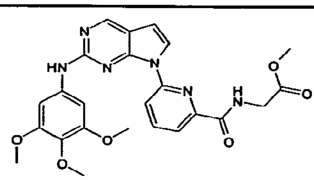
137		MS (*m/z*) 484.2 (M+1).
138		MS (*m/z*) 462.2 (M+1).
139		MS (*m/z*) 491.2 (M+1).
140		MS (*m/z*) 474.2 (M+1).
141		MS (*m/z*) 505.3(M+1).
142		MS (*m/z*) 519.2 (M+1).
143		MS (*m/z*) 407.3 (M+1).
144		MS (*m/z*) 419.2 (M+1).
145		MS (*m/z*) 491.2 (M+1).

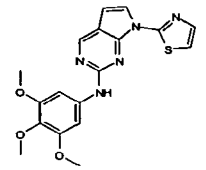
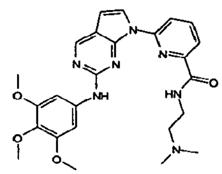
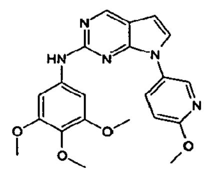
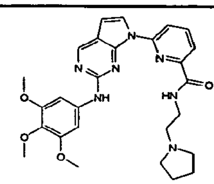
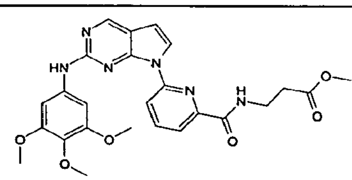
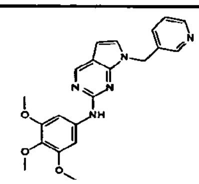
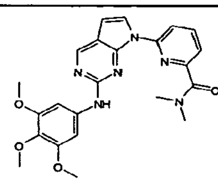
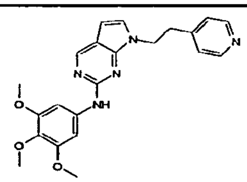
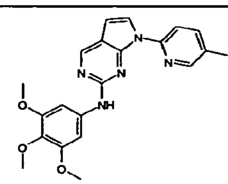
146		MS (*m/z*) 492.2 (M+1).
147		MS (*m/z*) 405.2 (M+1).
148		MS (*m/z*) 444.9 (M+1).
149		MS (*m/z*) 520.3 (M+1).
150		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.71 (s, 1H), 8.29 (t, 1H), 8.08 (m, 1H), 8.01 (m, 1H), 7.57 (t, 1H), 7.26 (d, 1H), 7.18 (s, 1H), 6.93 (s, 2H), 6.60 (d, 1H), 3.93 (s, 3H), 3.80 (d, 9H); MS (*m/z*) 435.3 (M+1).
151		MS (*m/z*) 445.1 (M+1).
152		^{1}H NMR 400 MHz ($CDCl_3$) δ 8.64 (s, 1H), 7.56 (m, 1H), 7.41 (m, 1H), 7.33 (t, 1H), 7.12 (m, 2H), 6.90 (s, 2H), 6.50 (d, 1H), 3.73 (s, 3H), 3.65 (s, 6H), 3.60 (s, 3H), 2.97 (m, 2H), 2.60 (m, 2H); MS (*m/z*) 463.1 (M+1).
153		MS (*m/z*) 478.2 (M+1).
154		MS (*m/z*) 423.1 (M+1).

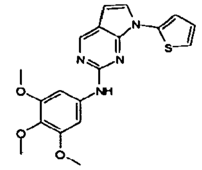
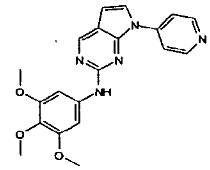
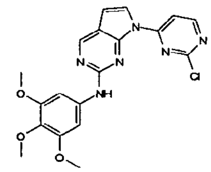
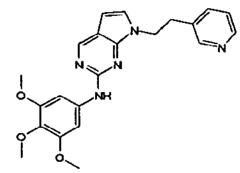
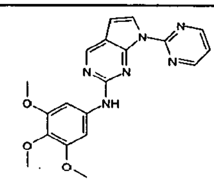
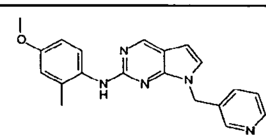
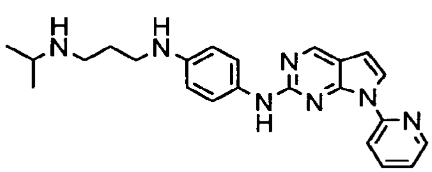
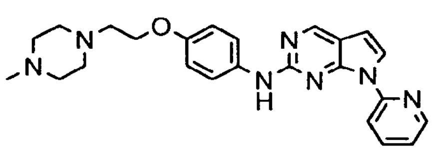
155		MS (*m/z*) 533.3 (M+1).
156		MS (*m/z*) 462.2 (M+1).
157		MS (*m/z*) 478.2 (M+1).
158		MS (*m/z*) 403.2 (M+1).
159		MS (*m/z*) 492.2 (M+1).
160		MS (*m/z*) 427.2 (M+1).
161		MS (*m/z*) 488.2 (M+1).
162		MS (*m/z*) 531.3 (M+1).
163		MS (*m/z*) 391.2 (M+1).

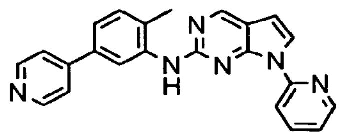
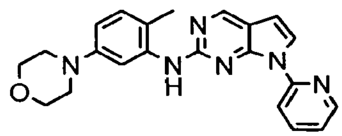
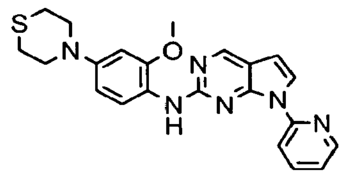
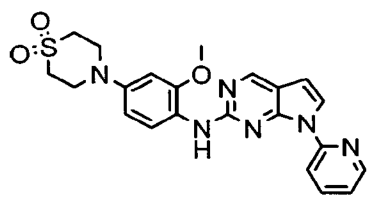
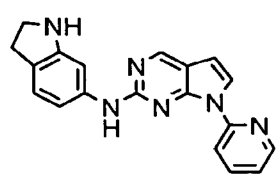
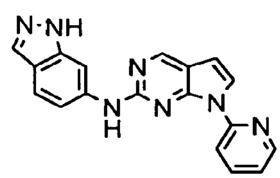
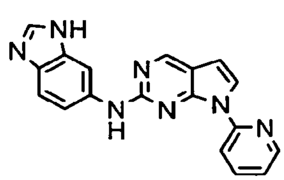
164		MS (*m/z*) 422.1 (M+1).
165		MS (*m/z*) 508.2 (M+1).
166		MS (*m/z*) 488.2 (M+1).
167		MS (*m/z*) 476.2 (M+1).
168		MS (*m/z*) 422.1 (M+1).
169		MS (*m/z*) 450.3 (M+1).
170		MS (*m/z*) 502.2 (M+1).
171		MS (*m/z*) 448.9 (M+1).
172		MS (*m/z*) 433.2M+1).

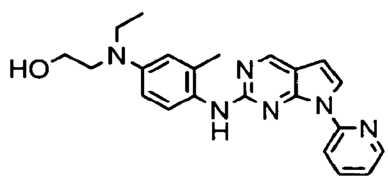
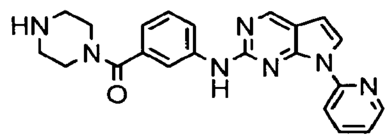
173		MS (*m/z*) 436.1 (M+1).
174		MS (*m/z*) 436.1 (M+1).
175		MS (*m/z*) 492.2 (M+1).
176		MS (*m/z*) 33.2 (M+1).
177		MS (*m/z*) 421.2 (M+1).
178		MS (*m/z*) 402.2 (M+1).
179		MS (*m/z*) 452.2 (M+1).
180		MS (*m/z*) 378.2 (M+1).
181		MS (*m/z*) 464.1 (M+1).

182		MS (*m/z*) 378.2 (M+1).
183		MS (*m/z*) 411.11 (M+1).
184		MS (*m/z*) 474.1 (M+1).
185		MS (*m/z*) 396.1 (M+1).
186		MS (*m/z*) 460.1 (M+1).
187		MS (*m/z*) 412.1 (M+1).
188		MS (*m/z*) 478.2 (M+1).
189		MS (*m/z*) 435.1 (M+1).
190		MS (*m/z*) 493.10 (M+1).

191		MS (*m/z*) 384.1 (M+1).
192		MS (*m/z*) 492.2 (M+1).
193		MS (*m/z*) 408.2 (M+1).
194		MS (*m/z*) 518.20 (M+1).
195		MS (*m/z*) 507.15 (M+1).
196		MS (*m/z*) 392.20 (M+1).
197		MS (*m/z*) 449.10 (M+1).
198		MS (*m/z*) 406.2 (M+1).
199		MS (*m/z*) 392.2 (M+1).

200		MS (*m/z*) 383.1 (M+1).
201		MS (*m/z*) 378.2 (M+1).
202		[1]H NMR 400 MHz ($CDCl_3$) δ 8.72 (d, 1H), 8.48 (s, 1H), 8.16 (d, 1H), 7.30 (d, 1H), 7.16 (s, 2H), 6.72 (d, 1H), 3.89 (s, 6H), 3.85 (s, 3H); MS (*m/z*) 413.1 (M+1).
203		MS (m/z) 406.3 (M+1).
204		[1]H NMR 400 MHz ($CDCl_3$) δ 8.85 (d, 2H), 8.74 (s, 1H), 8.03 (d, 1H), 7.32 (s, 1H), 7.25 (t, 1H), 7.13 (s, 2H), 6.63 (d, 1H), 3.93 (s, 6H), 3.86 (s, 3H); MS (*m/z*) 379.4 (M+1).
205		MS (*m/z*) 346.2 (M+1).
206		
208		

209		
210		
211		
212		
213		
214		
215		

216		
217		

Assays

Compounds of the present invention are assayed to measure their capacity to selectively inhibit cell proliferation of 32D cells expressing BCR-Abl (32D-p210) compared with parental 32D cells. Compounds selectively inhibiting the proliferation of these BCR-Abl transformed cells are tested for anti-proliferative activity on Ba/F3 cells expressing either wild type or the mutant forms of Bcr-abl. In addition, compounds are assayed to measure their capacity to inhibit b-Raf.

Inhibition of cellular BCR-Abl dependent proliferation (High Throughput method)

The murine cell line used is the 32D hemopoietic progenitor cell line transformed with BCR-Abl cDNA (32D-p210). These cells are maintained in RPMI/10% fetal calf serum (RPMI/FCS) supplemented with penicillin 50 μg/mL, streptomycin 50 μg/mL and L-glutamine 200 mM. Untransformed 32D cells are similarly maintained with the addition of 15% of WEHI conditioned medium as a source of IL3.

50 μl of a 32D or 32D-p210 cells suspension are plated in Greiner 384 well microplates (black) at a density of 5000 cells per well. 50nl of test compound (1 mM in DMSO stock solution) is added to each well (STI571 is included as a positive control). The cells are incubated for 72 hours at 37 °C, 5% CO_2. 10 μl of a 60% Alamar Blue solution (Tek diagnostics) is added to each well and the cells are incubated for an additional 24 hours. The fluorescence intensity (Excitation at 530 nm, Emission at 580 nm) is quantified using the Acquest™ system (Molecular Devices).

Inhibition of cellular BCR-Abl dependent proliferation

32D-p210 cells are plated into 96 well TC plates at a density of 15,000 cells per well. 50 μL of two fold serial dilutions of the test compound (C_{max} is 40 μM) are added to each well (STI571 is included as a positive control). After incubating the cells for 48 hours at 37 °C, 5% CO_2, 15 μL of MTT (Promega) is added to each well and the cells are incubated for an additional 5 hours. The optical density at 570nm is quantified spectrophotometrically and IC_{50} values, the concentration of compound required for 50% inhibition, determined from a dose response curve.

Effect on cell cycle distribution

32D and 32D-p210 cells are plated into 6 well TC plates at 2.5×10^6 cells per well in 5 ml of medium and test compound at 1 or 10 μM is added (STI571 is included as a control). The cells are then incubated for 24 or 48 hours at 37 °C, 5% CO_2. 2 ml of cell suspension is washed with PBS, fixed in 70% EtOH for 1 hour and treated with PBS/EDTA/RNase A for 30 minutes. Propidium iodide (Cf= 10 μg/ml) is added and the fluorescence intensity is quantified by flow cytometry on the FACScalibur™ system (BD Biosciences). Test compounds of the present invention demonstrate an apoptotic effect on the 32D-p210 cells but do not induce apoptosis in the 32D parental cells.

Effect on Cellular BCR-Abl Autophosphorylation

BCR-Abl autophosphorylation is quantified with capture Elisa using a c-abl specific capture antibody and an antiphosphotyrosine antibody. 32D-p210 cells are plated in 96 well TC plates at 2×10^5 cells per well in 50 μL of medium. 50 μL of two fold serial dilutions of test compounds (C_{max} is 10 μM) are added to each well (STI571 is included as a positive control). The cells are incubated for 90 minutes at 37 °C, 5% CO_2. The cells are then treated for 1 hour on ice with 150 μL of lysis buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 5 mM EDTA, 1 mM EGTA and 1% NP-40) containing protease and phosphatase inhibitors. 50 μL of cell lysate is added to 96 well optiplates previously coated with anti-abl specific antibody and blocked. The plates are incubated for 4 hours at 4 °C. After washing with TBS-Tween 20 buffer, 50 μL of alkaline-phosphatase conjugated anti-phosphotyrosine antibody is added and the plate is further incubated overnight at 4 °C. After washing with TBS-Tween 20 buffer, 90 μL of a luminescent substrate are added and the luminescence is quantified using the Acquest™ system (Molecular

Devices). Test compounds of the invention that inhibit the proliferation of the BCR-Abl expressing cells, inhibit the cellular BCR-Abl autophosphorylation in a dose-dependent manner.

Effect on proliferation of cells expressing mutant forms of Bcr-abl

Compounds of the invention are tested for their antiproliferative effect on Ba/F3 cells expressing either wild type or the mutant forms of BCR-Abl (G250E, E255V, T315I, F317L, M351T) that confers resistance or diminished sensitivity to STI571. The antiproliferative effect of these compounds on the mutant-BCR-Abl expressing cells and on the non transformed cells were tested at 10, 3.3, 1.1 and 0.37 μM as described above (in media lacking IL3). The IC_{50} values of the compounds lacking toxicity on the untransformed cells were determined from the dose response curves obtained as describe above.

Focal Adhesion Kinase (FAK) Inhibition

Compounds of the invention are tested for their ability to inhibit the activity of FAK. The FAK kinase activities are measured in 384-well plates using a time-resolved fluorescence resonance energy transfer (TR-FRET)-based assay method. Full length human FAK is expressed in E. Coli as a GST-tagged protein and purified by an immobilized glutathione column. A biotinylated peptide, biotin-SETDDYAEIID (Synthesized by SynPep Corp.), corresponding to the autophosphorylation site sequence of human FAK, is used as the substrate in the assay. E. Coli-expressed FAK kinase (2.4 μg/ml) is mixed together with FAK peptide (133 nM) in 15 μl of assay buffer (20mM Hepes, pH7.4, 5mM $MgCl_2$, 2mM $MnCl_2$, 0.5mM Na_3VO_4, 0.1% BSA, 0.1% TritonX-100). A compound of the invention (0.5 μl - dissolved in DMSO) is then added to the enzyme/peptide solution. After incubation at room temperature for 10 minutes, 5μl of 40μM ATP in assay buffer is added to initiate the reaction. The reaction mixture is incubated at room temperature for 2 hours. 50μl of detection reagents containing 0.15nM of Eu-labeled antiphosphotyrosine antibodies (PT66-Eu, PerkinElmer) and 1.5μg/ml of SA-APC (PerkinElmer) in detection buffer (10mM Tris-HCl, pH7.4, 6mM EDTA, 0.1% BSA, 0.1% TritonX-100) is then added. The mixture is incubated at room temperature for 30 minutes and the TR-FRET signals are measured using an Acquest plate reader (Molecular Device).

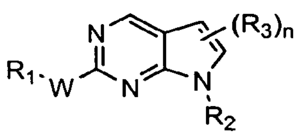
Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. For example, compounds of Formula I preferably show an IC_{50} in

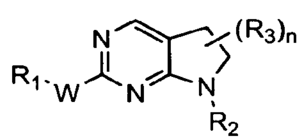
the range of 1 x 10^{-10} to 1 x 10^{-5} M, more preferably less than 500nM for Focal Adhesion Kinase (FAK).

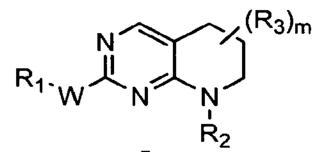
It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

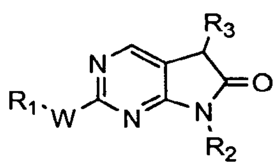
WE CLAIM:

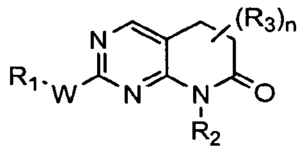
1. A compound chosen from Formula Ia, Ib, Ic, Id and Ie:


Ia


Ib


Ic


Id


Ie

in which:

n is chosen from 0, 1 and 2; m is chosen from 0, 1, 2 and 3;

W is chosen from $-NR_4-$, $-S-$, $-O-$, $-S(O)-$ and $-S(O)_2-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl;

R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-XNR_5R_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent of R_1 is further optionally substituted by 1 to 5 radicals independently chosen from C_{1-6}alkyl and C_{1-6}alkoxy;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl-C_{0-4}alkyl and C_{3-8}heterocycloalkyl-C_{0-4}alkyl; wherein any arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl of R_2 is optionally substituted by 1 to 3 radicals

independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XSNR_5R_5$, $-XS(O)NR_5R_5$, $-XS(O)_2NR_5R_5$, $-XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5R_5$, $-XC(O)NR_5XC(O)OR_5$, $-XC(O)NR_5XNR_5C(O)R_5$, $-XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XC(O)R_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; and R_7 is chosen from halo and cyano;

R_3 is chosen from halo, hydroxy, $-XSR_5$, $-XS(O)R_5$, $-XS(O)_2R_5$, $-XC(O)R_5$ and $-XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

W is chosen from $-NR_4-$ and $-O-$; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl;

R_1 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, C_{5-10}heteroaryl, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XNR_5XNR_5R_5$, $-XNR_5XOR_5$, $-XC(O)NR_5R_5$, $-XOXR_6$ and $-XC(O)R_6$; wherein X is a bond or C_{1-6}alkylene; R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; and R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; wherein any heteroaryl substituent of R_1 is further optionally substituted by 1 to 5 C_{1-6}alkyl radicals;

R_2 is chosen from C_{6-10}aryl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, C_{3-8}heteroarylC_{0-4}alkyl, $-XNR_5R_5$, $-XOR_5$, $-XSR_5$, $-XS(O)_2NR_5R_5$, $-XC(O)OR_5$, $-XOC(O)R_5$, $-XC(O)NR_5XNR_5R_5$, $-XC(O)NR_5XC(O)OR_5$, $-XC(O)NR_5XNR_5C(O)R_5$, –

$XC(O)NR_5XNR_5C(O)OR_5$, $-XC(O)NR_5XOR_5$, $-XC(O)N(XOR_5)_2$, $-XNR_5C(O)R_5$, $-XC(O)NR_5R_6$, $-XC(O)R_6$, $-XR_7$, $-XR_6$ and $-XC(O)NR_5XR_7$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; R_6 is chosen from C_{3-8}heterocycloalkyl-C_{0-4}alkyl and C_{5-10}heteroaryl-C_{0-4}alkyl optionally substituted by 1 to 3 radicals chosen from C_{1-6}alkyl and $-C(O)OH$; and R_7 is cyano; and

R_3 is chosen from halo, hydroxy, $-XC(O)R_5$ and $-XC(O)OR_5$; wherein X is a bond or C_{1-6}alkylene; and R_5 is chosen from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl.

3. The compound of claim 1 in which W is chosen from –NH– and –O–; and R_1 is chosen from phenyl, benzyl, 5,6,7,8-tetrahydro-naphthalenyl, benzo[1,3]dioxolyl, 1H-indazol-7-yl, indan-4-yl and 1H-indolyl; wherein any arylalkyl and heteroarylalkyl of R_1 is optionally substituted by 1 to 3 radicals independently chosen from methoxy, methyl, amino, halo, hydroxymethyl, hydroxy, quinoxalinyl, ethyl, pyridinyl, methoxy-phenyl, piperazinyl-carbonyl, ethyl-(2-hydroxy-ethyl)-amino 2-(4-methyl-piperazin-1-yl)-ethoxy, formamyl, isopropyl, methyl-sulfanyl, tri-fluoro-methyl, ethoxy, 3-isopropylamino-propylamino, dimethyl-amino, morpholino, cyclopropyl-methoxy, butoxy, cycloheptyl-oxy and 1,4,5,7-tetramethyl-pyrrolo[3,4-d]pyridazinyl.

4. The compound of claim 1 in which R_2 is chosen from pyridinyl, phenyl, thiazolyl, pyridinyl-methyl, pyridinyl-ethyl, thiophenyl, benzyl, quinolinyl, 7-oxo-5,6,7,8-tetrahydro-naphthalenyl, naphthyl and pyrimidinyl; wherein any arylalkyl or heteroarylalkyl of R_2 is optionally substituted by 1 to 3 radicals independently chosen from halo, nitro, cyano, methyl, propyl-sulfamoyl, methyl-sulfamoyl, methoxy, methyl-carboxy, 2-dimethylamino-ethyl-formamyl, carboxy, amino, cyano-ethyl, cyano-methyl, ethenyl, tri-fluoro-methyl, hydroxy-methyl, ethyl, methyl-sulfanyl, butyl, isobutyl, carboxy-methyl-formamidyl, 1-carboxy-ethyl-formamidyl, carboxy-ethyl, amino-ethyl-formamidyl, amino-propyl-formamidyl, dimethyl-amino-ethyl-formamidyl, dimethyl-amino-propyl-formamidyl, dimethyl-amino-butyl-formamidyl, methyl-formamidyl, ethyl-formamidyl, ethyl-formamidyl-methyl, 2-(2-dimethylamino-ethylcarbamoyl)-ethyl, 2-(2-dimethylamino-formamidyl)-ethyl, 2-(amino-ethyl-formamidyl)-ethyl, 2-(amino-propyl-formamidyl)-ethyl, 2-(propyl-formamidyl)-ethyl, amino-propyl-formamidyl-methyl, 2-(methyl-amino-carbamoyl)-ethyl, 2-(ethyl-amino-carbamoyl)-

ethyl, morpholino-ethyl-formamidyl, morpholino-carbonyl-methyl, amino-ethyl-formamidyl-methyl, cyclobutyl-formamidyl, methyl-formamidyl-methyl, dimethyl-formamidyl-methyl, hydroxy-ethyl-formamidyl-methyl, hydroxy-propyl-formamidyl-methyl, N,N-bis-(3-hydroxy-propyl)-formamidyl, cyclopentyl-formamidyl, isobutyl-formamidyl, isobutyl-formamidyl-methyl, cyclopentyl-formamidyl-methyl, cyano-ethyl-formamidyl, cyano-methyl-formamidyl, pyrrolidinyl-ethyl-formamidyl, 2-(isobutyl-formamidyl)-ethyl, 1H-tetrazolyl, 2-(1H-tetrazol-5-yl)-ethyl, 2-(1H-tetrazol-5-yl)-methyl, 2-(1-methyl-1H-tetrazol-5-yl)-methyl, acetyl-amino, cyclopropyl-formamidyl-methyl, hydroxy-ethyl-formamidyl, hydroxy-propyl-formamidyl, propyl-formamidyl-methyl, ethoxy-propyl-formamidyl, acetyl-amino-ethyl-formamidyl, 1-methyl-piperidin-4-yl-formamidyl, morpholino-carbonyl-ethyl, methoxy-carbonyl-methyl, methoxy-carbonyl-ethyl-formamidyl, methoxy-carbonyl-ethyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl-methyl, methoxy-carbonyl-methyl-formamidyl, 4-amino-cyclohexyl-formamidyl, 4-amino-cyclohexyl-formamidyl-methyl, acetyl-amino-ethyl-formamidyl-methyl, ethoxy-propyl-formamidyl-methyl, methoxy-carbonyl-ethyl, 1-formyl-pyrrolidin-2-yl-carboxylic acid, (1-carboxy-3-methyl-butyl)-formamidyl, 2-(methoxy-carbonyl-methyl-formamidyl)-ethyl, 1-carboxy-(2,2-dimethyl-propyl)-formamidyl, 3-tert-butoxycarbonyl-amino-propyl-formamidyl, acetoxy-methyl and 1-carboxy-ethyl-formamidyl.

5. The compound of claim 1 in which n is 0 or 1; m is 0 or 1; and R_3 is chosen from halo, hydroxy, $-C(O)OH$ and $-C(O)OCH_3$.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

7. A method for treating a disease in an animal in which inhibition of kinase activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

8. The method of claim 7 in which the kinase is chosen from FAK, c-Met, Abl, BCR-Abl, PDGF-R, c-Kit, trkB, FGFR3, Fes, Lck, Syk, b-RAF, MKK6 and SAPK2β.

9. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which the kinase activity of FAK, c-Met, Abl, BCR-Abl, PDGF-R, c-Kit, trkB, FGFR3, Fes, Lck, Syk, b-RAF, MKK6 and/or SAPK2β contributes to the pathology and/or symptomology of the disease.

COMPOUNDS AND COMPOSITIONS AS PROTEIN KINASE INHIBITORS

ABSTRACT OF THE DISCLOSURE

The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly diseases or disorders that involve abnormal activation of the FAK, c-Met, Abl, BCR-Abl, PDGF-R, c-Kit, trkB, FGFR3, Fes, Lck, Syk, b-RAF, MKK6 and SAPK2β kinases.